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The effect of coronary artery bypass graft operations on serum asprosin values

Asprosine and coronary artery bypass graft operations

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Abstract
Aim: The main purpose of this study was to investigate the effects of coronary artery bypass graft operations (CABGO) on serum asprosin levels.
Material and Methods: Twenty-five patients who underwent CABGO with the diagnosis of coronary artery disease (CAD) were included in the study. The patients were divided into three groups according to the study time: preoperative (preop), postoperative day 1 (postop1), and postoperative day 7 (postop7). The effects of the operation on asprosin levels were discussed in light of the literature data by evaluating fasting plasma asprosin levels for at least 8 hours in all three groups.
Results: There were 13 men and 12 women in the study group with a mean age of 64.4±9.9 years. It was found that the asprosin levels that were measured in the postop1 and postop7 groups were significantly higher than in the preop group (P<0.001). When the factors that affected the asprosin hormone levels at different times were examined, it was found that only the gender factor was significant (P=0.013). Although a significant increase was observed in postop7 and postop1 when compared to the preop value in both genders, a decrease was detected in postop7 when compared to postop1; and although this decrease was statistically significant in women (P=0.010), it was not significant in men (P=0650).
Discussion: In CABGO patients, increased serum asprosin levels are detected in the early postoperative period. This increase was more significant in women, which may be because of the protective effects of asprosin, which also has antioxidant features.

Keywords
Asprosin, Coronary Artery Disease, Coronary Artery Bypass, Graft

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Introduction

A new glycogenic adipokine was identified in 2016 by Romero et al. This hormone, which is encoded by two exons of the Fibrillin 1 gene, is secreted by White Adipose Tissue and regulates hepatic glucose secretion during fasting [1].

This hormone also stimulates the hypothalamic nutrition center, and causes appetite stimulation and fat storage [2]. The Fibrillin 1 gene, which is the source of asprosin, was isolated in various organs e.g. the heart, lung, and kidney. Studies also showed that pancreatic β cells can secrete asprosin under hyperlipidemic conditions [1,3].

Asprosin shows a functional contrast to insulin. Although low glucose levels increase its production, it is inhibited in the nutritional state. It was reported that the injection of recombinant asprosin caused a sudden glucose peak and hyperinsulinemia in experimental studies. Some clinical and experimental studies also showed that it is cardioprotective, and provides significant improvements in left ventricular ejection fraction contributing to wound healing [4,5].

This hormone that has a long history was accepted as a potential biomarker for abnormal glycolipid metabolic disorders e.g. obesity and Type 2 Diabetes. However, serum asprosin levels were not investigated in patients who were operated on for CAD. The purpose of the study was to investigate the effects of the operation on the asprosin levels in patients who undergo CABGO.

Material and Methods

This study was approved by Adıyaman University, Faculty of Medicine, Non-Invasive Clinical Research Ethics Committee (Decision Date: 20/03/2019; Decision Number: 2019/2-4).

The study was designed as a prospective self-match study. Written consent forms were obtained from all participants, and a total of 25 patients were included in the study between February 2019 and June 2019. Patients with a Body Mass Index (BMI) ≥30, diabetic, hyperlipidemic, liver failure, pancreatic acute-chronic disease, and acute infections were excluded from the study. Those who died in the first week were not included in the study. The patients were divided into three groups according to the study time as preoperative (preop), postoperative day 1 (postop1), and postoperative day 7 (postop7). At least 8 hours of fasting venous blood samples were taken from all three groups, and were centrifuged for 10 minutes at 1200gX3000rpm, then were separated and stored at -80°C until the analysis day. After the samples were taken from 25 patients at three different times (preop, postop1 and postop7), asprosin values were evaluated with the Homo Sapiens Asprosin Elisa Kit -SEA332Hu (26603 W. Fernhurst Dr., Unit 2201, Katy. TX77494, USA). The effects of Coronary Artery Bypass Graft Operation on FPA values were investigated by comparing the preop, postop day 1, postop day 7 and fasting daily plasma asprosin (FPA) values of the patients. Also, the relationship between asprosin and gender were evaluated by comparing the FPA values in each group and between the groups according to gender. Effects of age, BMI, Total Cholesterol (TC), Total Glyceride (TG), High-Density Lipoprotein-cholesterol (HDL), Low-Density Lipoprotein-cholesterol (LDL), and the number of bypassed vessels (CABGOx) on the FPA value were also investigated.

Statistical analyses

Mean±standard deviation was given as a descriptive value for quantitative variables and the number of patients (percentages) for qualitative variables. The distribution of the variables was checked with the Kolmogorov-Smirnov Test. The relations between the variables were evaluated with Pearson's Correlation Analysis. The Wilcoxon Test was used for repeated measurement analyses, and the Independent Simple T-Test was used for independent variables. The factors affecting the changes in Asprosin hormone were analyzed by using the Univariate Linear Regression Analysis. The IBM SPSS Statistics 22 was used for statistical analysis, and the statistical significance level was taken as 0.05.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A total of 25 patients (12 female, 13 male) were included in the study. The mean age was 64.4±9.9 years. The preparative demographic data of the patients are shown in Table 1.

Firstly, data were evaluated without considering gender and other independent variables to detect the effects of the operation on the FPA levels. The FPA value (12.27±3.48) that was measured for postop1 was found to be significantly higher than the preoperative FPA value (8.12±2.80) ($P<0.001$). The FPA value that was measured at postoperative 7 (11.50±2.92) was significantly higher than the preoperative FPA value ($p=0.002$). However, although the FPA value at postop7 (11.50±2.92) was lower than the postop1 value (12.27±3.48), which was not statistically significant ($p=0.112$) (Table 2).

The relationship between variables and preoperative FPA level was examined by Pearson's Correlation Analysis. A positive correlation was detected between gender, BMI, TC, TG, and CABGOx. This relation was particularly strong for gender and CABGOX [$r(23)=0.731$, $P<0.001$, $r(23)=0.825$, $P<0.001$, respectively].

Multivariate Linear Regression Analysis was made to examine the effects of the preoperative dependent variable on the independent variables of gender, BMI, TC, TG, and CABGOx. As a result of the analysis, the significant regression model, $F(5.19)= 24.19$, $P<0.001$, and 86% of the variance in the dependent variable (R^2adjusted=0.864) were confirmed with the independent variables. Preoperative FPA value for gender (ß= 0.403, $t(19)=2.24$, $P=0.037$, $pr2=0.25$), BMI (ß= 0.354, $t(19)=2.09$, $P=0.05$, $pr2=0.187$), and CABGOx (ß= 0.389, $t(19)=2.34$, $P=0.031$, $pr2=0.223$) were found. In this respect, a positive correlation was detected. However, the relationship between preoperative FPA and TC (β= -0.17, $t(19)=-0.153$ $P=0.88$, $pr^2=0.001$), and TG (β= 0.122, $t(19)=0.078$, $P=0.447$, $pr^2=0.031$) was not significant (Table 3).

The scatter plot of the Multiple Regression Analysis between the variables with preoperative FPA is summarized in Figure 1.

Risk factors that affected changes in Asprosin hormone with respect to time were examined with the Univariate Linear Regression Analysis, and only the gender variable was found to be significant. In this context, the fact that the gender was female instead of male increased the change in the FPA hormone by 1.857 units. Also, it has been observed that gender

alone explained 23.9% of the change in the FPA hormone. According to gender, the preop and postop 1st-day FPA values were higher in women on day 2 (P<0.001), and the difference between the genders was not significant on the postoperative day 7 (P=0.051). According to gender, there was a statistically significant increase in postop1 and postop7 in women when compared to pre-op values, and a significant decrease in postop7 compared to postop1 (P=0.002, P=0.002, P=0.010, respectively). Among the groups, postop1 and postop7 were significantly higher in males than preop values (P<0.001). Although there were decreases in postop7 in men when compared to postop1, and this was not statistically significant (P=0.650) (Table 2). The distribution of repeated measurements of the FPA hormone according to gender is summarized in Figure 2.

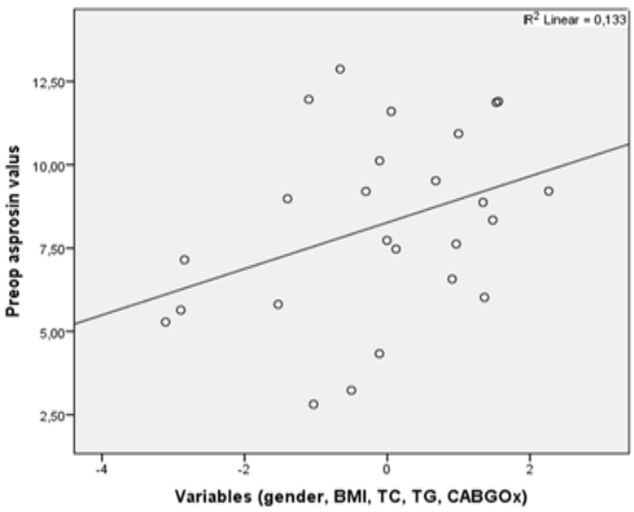

Figure 1. The distribution graph of preoperative asprosin value and variables. BMI: Body mass index, TC: Total cholesterol, TG: Triglyceride, CABGOx: Number of vessels of coronary artery bypass graft operation.

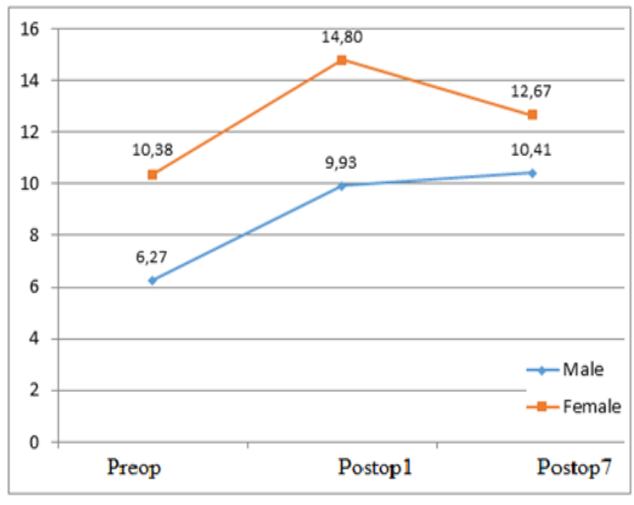

Figure 2. Distribution of Repeated Measurements of Asprosin Hormone according to Gender.

Table 1. Preoperative Demographic Values

		Min-Max	Median	Mean±SD/n(%)	P[T]
Gender	Female			12 (48)	0,503
	Male			13 (52)	
Age	Female	41-74	63	62,17±9.94	0,295
	Male	47-84	67	66.46±10,16	
Asprosin Value	Female	5,47-12,87	10,53	10.13±2,19	<0,001
	Male	2,81-9,21	6,02	6,27±2,05	
BMI (kg/m²)	Female	19,7-29,8	24,55	24,46±2,84	0,911
	Male	18,07-29,5	25,8	24,60±3,83	
TC (mg/dL)	Female	185-265	200.5	205,58±21,70	0,114
	Male	128-258	175	184,38±39,44	
TG (mg/dL)	Female	186-398	281,5	282,75±58,61	0,264
	Male	155-398	251	253,62±67,68	
HDL(mg/dL)	Female	27-47	35	35.83±6,90	0,824
	Male	25-48	35	35,23±6,51	
LDL(mg/dL)	Female	83-181	112,4	113,20±26,19	0,201
	Male	51,4-148,4	94,2	98,48±29,61	
CABGOx	Female	2.3			<0,001
	Male	3.5			

SD:Standard deviation, Min:Minimum, Max:Maximum, TIndependent sample t-test , BMI: Body mass index, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, CABGOx: Number of vessels of coronary artery bypass graft operation

Table 2. Intra and intergroup asprosin values

		Min-Max	Median	Mean±SD	P	P*	PΨ
Preop	Total	2,81-12,87	8,87	8,12±2,80			
	Female	5,47-12,87	10,54	10.13±2,19	<0.001[t]		
	Male	2,81-9,21	6,02	6,27±2,05			
Postop1	Total	6,32-21,01	11,52	12,27±3,48		<0,001[w]	
	Female	9,66-21,01	4,99	14,80±2,92	<0.001[t]	0,002[w]	
	Male	6,32-14,25	9,9	9,93±2,04		<0,001[w]	
Postop7	Total	5,04-17,99	11,75	11,50±2,92		0,002[w]	0,112[w]
	Female	7,89-17,99	12,79	12,67±2,60	0.051[t]	0,002[w]	0,010[w]
	Male	5,04-16,23	10,53	10,41±2,86		<0,001[w]	0,650[w]

[t]Independent sample t-test , [w]Wilcoxon test/ *Difference with preop/ [Ψ]Difference with postop1, SD:Standard deviation, Min:Minimum, Max:Maximum

Table 3. Multivariate logistic regression analysis made between preoperative asprosin and variables.

Model	β	t	p value	95,0% CI for B		C	CS
				Lower	Upper	Partial	VIF
(Constant)		-3,09	0,006	-11,62	-2,235		
Gender	0,403	2,242	0,037	0,147	4,298	0,457	4,525
BMI	0,354	2,089	0,05	-0,001	0,584	0,432	4,02
TC	-0,017	-0,153	0,88	-0,021	0,018	-0,035	1,76
TG	0,122	0,777	0,447	-0,009	0,02	0,175	3,473
CABGOx	0,389	2,336	0,031	0,11	2,012	0,472	3,873

β: Beta coefficient, CI: Confidence Interval, C: Correlations, CS: Collinearity Statistics, BMI: Body mass index, TC: Total cholesterol, TG: Triglyceride, CABGOx: Number of vessels of coronary artery bypass graft operation

Discussion

To the best of our knowledge, our study is the first one in the literature to examine FPA levels in patients with operated Coronary Artery Disease. In our study, it was observed that the FPA levels increased in the early postoperative first week in patients with CABGO and the diagnosis of CAD. It was shown in our study that FPA values were increased in the early postoperative period compared to the preoperative period in patients with CABGO, regardless of the variables. This increase was especially significant on the first postoperative day. It was also observed that there were significant increases on postoperative day 7 compared to the preoperative period. However, it was also observed that there was a slight decrease in postop7 compared to postop1 in the entire patient population. Although this decrease was significant in females, it was not at statistically significant levels in males. Another important finding of our study was that preoperative FPA values had a positive relation with the number of diseased arteries in CAD. A similar relation was also detected between BMI and female gender, which is consistent with the literature data. A positive and linear relation was detected between the female gender and BMI and FPA.

Asprosin is a peptide glycogenic hormone, which stimulates glucose release from the liver by affecting OLFR734 receptors. This effect is limited to hepatic glucose production, independent of insulin levels. In normal healthy individuals, the normal FPA level in women was between 4.02 ± 0.49 nmol/L, and 5.94 ± 3.04 nmol/L in men [6].

The levels decrease in the presence of high insulin and glucose levels (in the case of satiety). In the first years after its discovery, it was shown in previous studies that the target organ was the liver. However, in studies conducted later, the asprosin receptor (OLFR734) was expressed outside the liver, in kidney cells, adipose tissues, olfactory nerves, testicular cells, and muscle tissues [7].

Asprosin levels have a circadian rhythm. Studies conducted on humans and experimental animals have shown that although its levels increase at night (in case of fasting), they decrease after a meal. It has been shown to increase appetite by crossing the blood-brain barrier in rodents [4,8].

Although its levels increase in obesity, insulin resistance, Type-1 and Type-2 diabetic patients, anorexia nervosa, gestational diabetes, and preeclampsia, its levels have been shown to decrease in neonatal progeroid syndrome, anorectic oncological patients, acromegaly, and streptozocin-induced diabetic mice [4].

A clinical study (in addition to animal experiments) that reported direct relations between serum asprosin and coronary artery stenosis in people with acute coronary syndrome with unstable angina pectoris showed that there was a significant and positive relation in this respect, and asprosin may be the first biochemical marker to predict severity [9,10].

In our study, it was shown that there is a positive and linear relationship between preoperative asprosin levels and female gender, BMI, TC, and TG. In other words, CADs that have high TC, TG, BMI, and female gender showed high preoperative asprosin levels. These results were in agreement with the literature data. Also, the number of bypassed coronary arteries was associated with higher preoperative asprosin levels.

A systemic inflammatory response occurs in cardiac surgeries that are carried out with extracorporeal circulation. Ischemia-reperfusion injury, contact of blood with non-endothelial circuits, cellular traumas because of surgical manipulations, oxidative stress, activation of the complement, and coagulation cascade are the causes of this inflammatory response. All these results might end up in cellular, and then, organ damage [11]. It was found in the literature review that the cardioprotective effect of asprosin was demonstrated in a study that investigated the effects of mesenchymal stromal cells previously treated with asprosin on the myocardium. It has also been shown to act by preventing H_2O_2-mediated apoptosis [12].

It was observed in the present study that the FPA levels increased in the first week in patients who underwent CABGO compared to the preoperative period, which was more significant on the first postoperative day. This is likely to be associated with the cardiac protective effects of asprosin, which has anti-inflammatory features. However, further studies are required to support this hypothesis. This increase in asprosin was higher in women than in men, which seems difficult to explain with the findings of our study. New studies that will be supported by a larger patient population and experimental studies will better shed light on the many mysteries of asprosin.

Study limitations

The main limitations of this study are the small number of patients, the use of single hospital data in the study. The limited number of studies in the literature on the cardioprotective effects of asprosin can be counted among the limitations of the study.

Conclusion

As a conclusion, an increase was detected in FPA values in the first week in operated CAD. Although this increase showed a decrease in the measurements after one week, it was still higher than the preoperative period. Based on the data obtained from the literature review we believe that this increase can be associated with the antioxidant cardioprotective effects of FPA. However, more extensive and experimental studies are needed to prove this.

The present study had several limitations. The first was the low patient population. The second was that only 3 measurements were made in the patients. We believe that controlled and experimental studies may provide more precise results to examine the protective effects of PFA against the negative cardiac effects of extracorporeal circulation with daily serial measurements.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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